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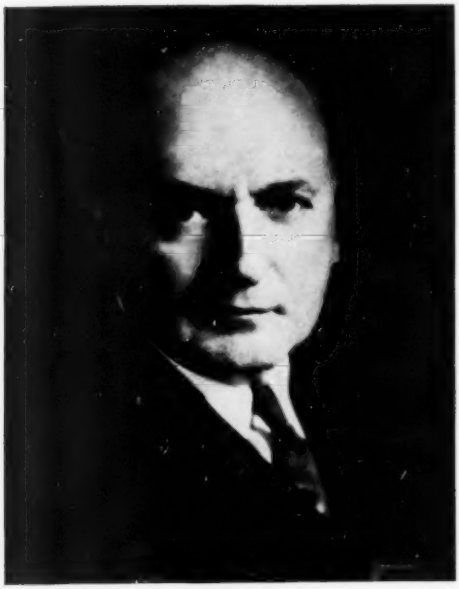

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OUR COVER

THE 1953 Remington Medalist, Dr. Hugh C. Muldoon, is a man well known in American Pharmacy and surely deserving of Pharmacy's highest award.

Dr. Muldoon began his study of pharmacy at the Albany College of Pharmacy where he later became Dean. He also received degrees from Valparaiso University and was for a time a member of its faculty. He served also on the staff of the Massachusetts College of Pharmacy. In 1925 Dr. Muldoon founded the School of Pharmacy at Duquesne University and he still heads this institution.

Dr. Muldoon has been most active in pharmaceutical affairs, on a national level as well as in Pennsylvania. In all of his activities and contacts he has commanded the respect and affection of all who knew him and worked with him. He has held many high offices including that of President of the American Association of Colleges of Pharmacy. In 1949, Dr. Muldoon was a member of the A. Ph. A. Mission to Japan sent by the United States. Last year he served as Chairman of the Committee on Centennial Celebration for the one hundredth anniversary in Philadelphia of the founding of the A. Ph. A.

Dr. Muldoon is the author of several texts, notably in the fields of organic chemistry and Pharmaceutical Latin. He also edits *The Science Counselor* a periodical well known to High School science teachers.

This year's Remington Medalist is best characterized as not only one of Pharmacy's best known educators but one of its most cultured and distinguished gentlemen.

E D I T O R I A L

ENGLAND ADOPTS THE METRIC SYSTEM

MOST Americans are accustomed to thinking of the British as conservative to the extreme, and the last to discard traditional methods and customs. It comes as a shock then to learn that in England, now, all drugs are being supplied by manufacturers in metric quantities! The old Imperial System, long dear to our English cousins and as unwieldy as our own Apothecaries' System, is used no more, at least in buying drugs from suppliers.

This innovation came about as the result of the visit to the United States of a productivity team sent from England. Following such a recommendation from this team, it was put into effect by the Association of British Pharmaceutical Industry. One of the great advantages cited was that of improving Britain's competitive position in the overseas drug market. Few countries in the world use other than the metric system in all transactions, wholesale and retail.

As a result of this step overtures have been made to the British Glass Manufacturers' Federation that they consider standardizing bottles and bottle sizes in metric units to still further streamline the complete conversion to the metric system.

After reading of these progressive steps taken in England the editor feels that possibly we should send a productivity team there. Surely many similar changes are long over-due here. The compounded confusion which rules here in drug metrology would be uncomprehensibly inept were we not accustomed to it from our youth. Almost all drugs are sold in bulk here using the Avoirdupois System for solids and the Apothecaries' for liquids. A few very expensive drugs are sold by the gram or cubic centimeter. The manufacturer often as not uses all three systems concurrently in preparing his private formulas. The pharmacist uses the Metric exclusively for manufacturing but dispenses in both Apothecaries and Metric. New drugs are usually packaged in metric quantities if dry and Apothecaries' if liquid, while old drugs are still supplied in Apothecaries' units. Thus digitalis leaf is packaged in 1½ grain tablets while an antihistamine tablet would be 25 or 50 mg. The same drug, however, in

an elixir would be supplied in pint bottles with the dose described as a teaspoonful and written by the physician as a fluidrachm. Need we say more?

To go from the ridiculous to the sublime, the U. S. P. XV proposes to use the Liter and milliliter (ml.) in place of 1000 cubic centimeters and cubic centimeter (cc.) used in the last several revisions. While this is more precise since the Liter is the proper standard of volume, it seems almost laughable in view of the utter confusion in our whole drug industry.

There are positive forces at work, however. New drugs are packaged in metric doses. The official compendia give precedence to the dose in metric quantities, the Apothecaries' equivalent being given in parentheses. Most medical schools now teach only metric doses and so on.

Much more rapid progress could be made, particularly if metric stock and prescription bottles were available. The glass industry should consider this need. The pioneer in meeting the need will in time be richly rewarded for his investment and foresight. Think of the fine promotional job that awaits such a development. Every medical school and college of pharmacy would endorse the idea and become ardent supporters. Most educators detest our present confusion and the resultant trials and tribulations inflicted on the student and young practitioner. Things are sufficently complex today in areas that cannot be simplified. To cling to an outdated metrology is both stupid and dangerous.

L. F. Tice

SPERMICIDAL ACTION OF KHELLIN

By Vinton R. Swayne and Gustav J. Martin *

EXTENSION of studies recently reported from this laboratory (1) relating to the spermicidal activity of a group of substances led to the discovery that khellin, derived from the seeds and fruits of Ammi visnaga, is a particularly powerful inhibitor of sperm motility.

This furanochromone, long used in Egypt as an antispasmodic, has been shown to have a selective action on the smooth muscle of the ureters, the bronchii and the bile ducts (2). It is not a sympatholytic (3) but does possess central nervous system depressant (5) and antihistaminic (4) effects. The demonstration that khellin increases markedly coronary blood flow (4, 6) led to its use in angina pectoris (7) and subsequently to application in the treatment of bronchial asthma.

Experimental

In vitro

Healthy, untreated male rats were etherized, their testes rapidly excised, the contents removed with a platinum wire loop and flushed in 0.08 ml. of the testing solution which contained approximately 2.5 mg. of test substance per ml. All solutions were made up in Locke Ringer's solution buffered at pH 7.4. The motile sperm were counted after 30 minutes. No stain was used.

In vivo

Twenty-one adult Wistar strain female rats were divided into groups of three. One male was introduced to each cage and then rotated weekly for the eight-week experimental period. For two weeks previous to and during the experimental period, the stock diet supplied to both sexes was mixed with a concentration of khellin such that each rat would ingest approximately 50 mg. of khellin daily per kg. of body weight.

Within a week the animals began to show signs of toxicity as indicated by decreased weight gains. The dosage was reduced to 25 mg./kg. and the males only were treated. Also, the number of females serviced by each male was reduced from three to two.

Results

In vitro

The results are tabulated:

* Research Laboratories, The National Drug Company, Phila., Pa.

TABLE I

In Vitro Spermicidal Power of Khellin and Related Molecules

	1:400	1:1000	1:4000	1:10,000	1:40,000	1:100,000	1:400,000	1:1,000,000	1:10,000,000	Control
Khellin				2—		2+		3+	0	0
Khellin				0		2—		4+		2—
Khellin				1+		2—		3+	2—	2—
2-methyl 3, 6, 7 trihydroxychalcone		4+		2+		1+		1+		1+
Ammi visnaga Khellin fraction	5+		4+		0					0
Ammi visnaga Khellin fraction	4+		2—		1+		1+			1+
Visnagan (crude)	5+		4+		1+		0			1+
Visnagan cryst. byproduct	4+		1+		1+		1+			1+
Ammi visnagin (fixed oil)	3+		1+		1+		1+			1+

Key to Chart:

Sperm sluggish	1—
Few dead in field	1+
10% " " "	2—
20% " " "	2+
50% " " "	3+
80% " " "	4+
100% " " "	5+

Visammidin, 2-methyl-5, 8-dimethoxy chromone, crystalline by products of khellin and visnagin were inactive.

TABLE II

COMPARISON OF IN VITRO MINIMUM EFFECTIVE SPERMICIDAL CONCENTRATIONS (M. E. C.)

Compound	M. E. C. (mg./cc.)
Khellin	0.001
phenyl mercuric nitrate	0.01
Visnagan (crude)	0.025
oxyquinoline sulfate	0.1
2-methyl 3, 6, 7 trihydroxy chromone	1.0
Lactic acid	1.0

In vivo

At a dosage of 50 mg. khellin/kg. body weight only eight of the twenty-one rats (38%) became pregnant, 12 did not and one was found dead.

Of those receiving 25 mg./kg. twenty-five of the thirty-nine experimental animals delivered (64%), while thirteen of the nineteen controls (69%) also became pregnant.

At the reduced dosage the animals appeared to be in perfect health, in contrast with those receiving 50 mg.

Discussion

Clearly, khellin is a powerful spermicide. The table of minimum effective concentrations shows it to be ten times more potent than phenyl mercuric nitrate which has long been considered to be the sine qua non for spermicidal preparations. Khellin showed no anti-fertility activity when fed to rats. The decreased fertility of the rats receiving 50 mg./kg. is believed to be an effect of toxicity.

It is difficult to provide a rationale for the spermicidal activity of khellin. Khellin, 2-methyl-3,6,7-trihydroxy chromone, the chalcones (1) and quinones (8)—all good spermicides—are also strong reducing substances. This might provide an explanation, for the motility of sperm is highly dependent upon a high level of glycolysis (9) (10). Anything interfering with this process or electron transport would reduce or abolish viability. The structure of visnagan has not

yet been established but it is known to have good reducing properties (11). Visnagin, which has no spermicidal activity, differs from khellin only in that it lacks one methoxyl group.

It is noteworthy that khellin was most effective at higher dilutions. This behavior is not without parallel in the realm of physiology, viz. effect of concentration of epinephrine on rate of urine formation. The active compounds related to khellin are effective at higher concentrations only. Thus it is possible that some khellin contaminated the solutions and thereby inhibited motility.

These encouraging results with khellin used therapeutically for centuries indicate a clinical trial.

Summary

Khellin has been shown to be ten times more spermicidal in vitro than phenyl mercuric nitrate. When fed to rats it had no effect on fertility. A clinical trial seems warranted.

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A BUFFERED SOLUTION OF SULFATHIAZOLE SODIUM FOR PARENTERAL OR OPHTHALMIC USE

By Marvin J. Silverman, Elsa Ehrenstein, and William E. Gordon, Jr. †

IT is generally agreed that, if possible, parenteral and ophthalmic solutions should be adjusted to the approximate pH of the blood, which is about 7.4. For 5% solutions of sulfathiazole sodium and sulfadiazine sodium, which have a pH between 9 and 10, Hind and Goyan (1), in their work on ophthalmic buffers, suggested a buffer solution of low capacity, consisting essentially of a dilution of 1 part of Palitzsch's pH 8.6 buffer solution with four parts of distilled water. This reduced the alkalinity to a safe minimum, the critical point before precipitation of free sulfonamide being reported as pH 8.2. The authors' experiments of 1951-52 showed this critical point to be pH 8.6 with the ordinary buffer systems. From this work, however, was developed a formula for sulfathiazole sodium solutions at a pH of 7.5, determined by the use of the Beckman pH meter. The formula is as follows:

Sulfathiazole Sodium	5 Gm.
Water for Injection	10 cc.
Polyethylene Glycol 400	35 cc.
* Sørensen's Acid Phosphate Soltion qs. ad.	100 cc.

* Sodium Acid Phosphate (monohydrated)	9.2 Gm.
Water for Injection qs. ad.	1000. cc.

Experimental

The solution prepared was colorless. Samples were kept in direct sunlight, others in total darkness. Those exposed to light developed a gradually deepening yellow color within a few weeks,

† Department of Pharmacy, Philadelphia College of Pharmacy & Science.

whereas the samples kept in the dark remained colorless for approximately one to one and a half months. The pH was checked frequently, and even after a deep yellow color had developed remained at 7.5.

Studies by T. D. Whittet (2) on the effect of the replacement of air with nitrogen in ampuls containing solutions of the sodium salts of sulfacetimide and sulfathiazole showed that darkening was retarded but not prevented. The retarding effect was somewhat greater with sulfacetimide than with sulfathiazole. Previous experience had shown that 0.5% of sodium metabisulfite would prevent discoloration of solutions of sulfacetimide for about a year when stored in diffused light but provided no protection in direct sunlight. Whittet thus suggested there would appear to be a two-fold cause for the discoloration in solutions of sulfacetimide, and possibly in sulfathiazole—oxidation and the action of direct sunlight. Studies on the discolored solutions of sulfonamides seemed to indicate that there was no significant increase in toxicity nor decrease in activity of the discolored solutions as compared with the fresh, colorless solutions.

Ampuls of sulfonamide solutions showed appreciable darkening following autoclaving at 115° C. for thirty minutes when the ampuls were air-filled, but there was no appreciable change when the ampuls were nitrogen-filled (2).

Ampuls containing 5% sulfathiazole sodium in the special vehicle, at pH 7.5, were separated into two batches. One batch was air-filled, while the other filled under nitrogen. Samples of each batch were removed and kept for longer term stability tests. The remainder of the lot was autoclaved at 121° C. for twenty minutes. The air-filled samples turned a deep yellow as a result of autoclaving. The nitrogen-filled ampuls turned a pale yellow. The pH of the solution remained unchanged following autoclaving.

After sixty days, the unautoclaved samples filled under nitrogen showed only a slight yellowish color, whereas those filled under air showed a definite yellow color. The autoclaved samples showed a slight deepening of color. The pH of both the autoclaved and unautoclaved samples remained at 7.5.

Recent studies by Kostenbauder, et al., (3) indicate that the salts of sulfathiazole and sulfadiazine are not chemically incompatible with borate buffers, but that their precipitation in such buffers is merely a function of the pH of the solution. In such buffers, only 2% sulfathiazole sodium is soluble at pH 8.6. In order to obtain a 5%

solution, they suggest that a pH of 8.97 is necessary for complete solubility of sulfathiazole sodium.

Irritation Studies

Four albino rabbits were utilized for tests to determine irritant properties of the final preparation and of individual components. Solutions used were as follows:

#1. Sørensen's Acid Phosphate solution

#2. Polyethylene Glycol 400

#3. Sørensen's Solution—60 parts
Polyethylene Glycol 400—40 parts

#4. The complete sulfathiazole sodium solution (pH 7.5)

The rabbits were marked for identification purposes, and five drops of each solution were instilled into the left eye of the particular animal being used for that solution. The right eye in each rabbit was left untouched for control purposes. Drops were instilled four times a day for a period of fourteen days. Examination of the rabbits' eyes was made both grossly and with the aid of an ophthalmoscope.

No change was evidenced in the rabbits subjected to solutions #1, 3, and 4, when compared to the control eye.

Solution #2, Polyethylene Glycol 400, elicited a response in the form of a slight chemosis. This evidence of irritation disappeared within twenty-four hours following cessation of application. However, the use of Polyethylene Glycol 400 as such is not recommended.

At a later date, a similar test was conducted over a period of seven days, utilizing as test samples, sulfathiazole sodium solutions in the suggested vehicle, which had been stored for several months and had developed a deep yellow color.

Three albino rabbits were subjected to the test in similar fashion. The results were negative in all three rabbits indicating that the change in coler of the solution caused no increase in irritation.

The concentration of the solution was checked by the diazotization method of the U. S. P. XIV.

Summary

1. A formula is offered whereby sulfathiazole sodium solutions are maintained at pH 7.5.

2. Discoloration of solutions on standing appear to be due to oxidation and action of direct sunlight.

3. No change in pH of the solution occurs following autoclaving or the appearance of a yellow color.

4. The solution causes no irritation when instilled into the eyes of rabbits over a period of two weeks.

5. The appearance of a yellow color in the solution neither decreases therapeutic effect nor increases irritation of the sulfathiazole sodium solution.

6. The solution may be assayed by the U. S. P. XIV method.

Acknowledgments

The authors wish to thank Mr. David Mayron, of the Graduate School of the Philadelphia College of Pharmacy and Science, for his efforts in the formulation and trial of this solution.

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THE ANTI-FUNGAL ACTIVITY OF AN AQUEOUS EXTRACT OF OSAGE ORANGE WOOD *

By Charles F. Peterson † and Eugene W. Brockemeyer ‡

THE hot water extract of the wood of *Maclura Pomifera* has been used as a native dye for a number of years. Furry in 1945 (1) found that a number of these dyes gave good to excellent protection against mildew. Our interest in this product was to compare its activity with other compounds for antifungal activity as compounded into various ointment bases, particularly against a causative organism of "Athlete's Foot."

Experimental

The Osage Orange Wood extract: The dried osage orange wood was extracted successively three times with distilled water heated to 95° C. The combined percolates were evaporated on a steam bath to yield a red-brown amorphous mass. (Yield, 6%)

Fungicidal Evaluation: The compounds were tested using the technique reported by Golden and Oster (2) using *Trichophyton mentagrophytes* (#670 Emmons).[1] The compounds which were insoluble in alcohol in the desired concentration were dissolved in acetone or water. The principle of this technique is the exposure of a disk of the culture to a solution of the agent for one minute, washing the agent from the disk, and then placing it in a culture media to await growth. The results are reported as the maximum nonfungicidal concentration and the minimum fungicidal concentration, Table No. 1.

The critical concentrations reported in the Table No. 1 were established from three parallel tests after three weeks incubation.

The osage orange extract was not fungicidal in the highest concentration possible. The commercial product was obtained from the American Dyewood Company, New York City. The commercial orange wood extract differed in that it was a honey-like mass. Neither extract showed fungicidal activity even when the one minute contact time was extended to 15 minutes.

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† School of Pharmacy, University of Kansas; †† College of Pharmacy, Ohio State University.

* Abstracted from a thesis submitted to the Graduate School, University of Kansas, by Eugene W. Brockemeyer in partial fulfillment of the requirements for the degree of Master of Science. Presented before the Pharmacy Subsection (Np), A A A S, December 29, 1952.

1. Courtesy of the Mycology Department, University of Kansas.

TABLE NO. 1

FUNGICIDAL ACTIVITY

Compound and Solvent	Maximum Nonfungicidal Concentration	Minimum Fungicidal Concentration
Salicylanilide in alcohol	1.5%	2.0%
3-Phenylsalicylic acid [2] in acetone	1.5%	2.0%
Undecylenic acid in water with 1% Tween 20 [3]	2.0%	2.5%
Undecylenic acid in acetone	2.0%	2.5%
Undecylenic acid in alcohol	2.5%	3.0%
Copper 3-Phenylsalicylic acid [2] in acetone	4.0%	5.0%
Osage Orange Extract in water	15.0%	*

Preparation of Ointment Bases.—The six different ointment bases used in fungistatic evaluation were prepared according to the following formulas: Hydrophilic Ointment, Hydrophilic Petrolatum, White Ointment, Petrolatum Rose Water Ointment,[4] Polyethylene Glycol Ointment, U. S. P. XIV, and Vanishing Cream prepared by the formula given below.

Stearic Acid	150 Gm.
White Wax	50 Gm.
Span 80 [5]	15 Gm.
Propylene Glycol	200 Gm.
Tween 80 [5]	85 Gm.
Water	500 Gm.
To make	1000 Gm.

* not fungicidal in the highest concentration possible.
2. From Dow Chemical Company, Midland, Michigan.
3. Tween 80 was also tested with identical results.
4. The rose oil was omitted.
5. Atlas Powder Company, Wilmington, Delaware.

Fungistatic Evaluation.—Petri dishes containing 18 cc. of Sabouraud's agar and 2 cc. of sterile horse serum were streaked with a ten-day-old culture of *Trichophyton mentagrophytes* (#670 Emmons) by means of a sterile cotton swab. A glass cylinder 5 mm. in height and 20 mm. (inside diameter), was filled with the ointment containing the test compound and placed flat in the center of the plate upon the agar surface to insure good contact between the ointment and the agar. The plates were incubated at 28° ± 1° C. for five days and then read for the zone of inhibition.

The inhibition of growth around the disk is reported (Table No. 2) as millimeters from the edge of the disk to the periphery of the cleared zone (the average of three measurements.) The concentration of the drug in the ointment was determined from minimum non-fungicidal concentration and the concentration most likely to be used in therapy.

TABLE NO. 2

ORDER OF FUNGISTATIC ACTIVITY

Compound	Ointment Base	Zone of Inhibition
15% Salicylic acid	Polyethylene Glycol Ointment	16.2 mm.
20% Osage Orange Extract	Vanishing Cream	12.3
5% Salicylanilide	Polyethylene Glycol Ointment	11.2
5% Undecylenic acid	Polyethylene Glycol Ointment	10.6
5% Undecylenic acid	Petrolatum Rose Water Ointment	9.2
5% Undecylenic acid	White Ointment	8.0
8% Copper 3-Phenylsalicylic acid	Polyethylene Glycol Ointment	8.0
5% 3-Phenylsalicylic acid	Polyethylene Glycol Ointment	6.6
5% Salicylanilide	Hydrophilic Ointment	6.4
15% Salicylic acid	Vanishing Cream	6.3
20% Zinc Undecylenate and 5% Undecylenic acid	Polyethylene Glycol Ointment	6.0
5% Undecylenic acid	Hydrophilic Petrolatum	5.4

Compound	Ointment Base	Zone of Inhibition
5% Salicylanilide	Petrolatum Rose Water Ointment	5.3
8% Copper 3-Phenylsalicylic acid	Hydrophilic Ointment	5.1
20% Osage Orange Extract	Hydrophilic Ointment	5.0
20% Zinc Undecylenate and 5% Undecylenic acid	Petrolatum Rose Water Ointment	5.0
10% Copper Undecylenate	Polyethylene Glycol Ointment	4.8
20% Zinc Undecylenate	Vanishing Cream	4.7
10% Copper Undecylenate	Vanishing Cream	4.7
20% Zinc Undecylenate and 5% Undecylenic acid	Hydrophilic Petrolatum	4.7
5% Salicylanilide	Vanishing Cream	4.7
5% Salicylanilide	White Ointment	4.5
10% Copper Undecylenate	Hydrophilic Ointment	4.3
20% Zinc Undecylenate and 5% Undecylenic acid	Hydrophilic Ointment	4.3
20% Zinc Undecylenate and 5% Undecylenic acid	Vanishing Cream	4.3
5% Undecylenic acid	Hydrophilic Ointment	4.2
20% Zinc Undecylenate and 5% Undecylenic acid	White Ointment	4.0
15% Salicylic acid	Petrolatum Rose Water Ointment	3.8
5% Salicylanilide	Hydrophilic Petrolatum	3.7
5% Undecylenic acid	Vanishing Cream	3.7
8% Copper 3-phenylsalicylate	Vanishing Cream	3.3
20% Osage Orange Extract (American Dyewood Co.)	Vanishing Cream	3.2

Table No. 2 lists the ointments in their order of activity. It will be noted that only the 5% undecylenic acid and 5% salicylanilide ointments are active in each ointment base (zone of inhibition greater than 3 mm.). Salicylic acid 15% is inactive in White Ointment and Hydrophilic Petrolatum, and slightly active in Hydrophilic Ointment.

Some of the ointments which showed activity were allowed to remain in the incubator for an additional ten days. The readings were taken for the zones of inhibition and reported in Table No. 3. None

of the zones of inhibition increased, but a number decreased notably. Undecylenic acid, zinc undecylenate, copper undecylenate, salicylic acid in Petrolatum Rose Water Ointment and the 3-phenylsalicylic acid ointments showed a definite decrease in activity.

To determine the effect of pH on fungistatic activity, seven compounds were tested by incorporating one part of buffering solution into three parts of Hydrophilic Ointment and Hydrophilic Petrolatum. The buffered vanishing cream was prepared by replacing one-half of the water with the buffer solution. Clark and Lubs' potassium biphosphate-sodium hydroxide buffering solutions (3) were used (pH 6, 7, 8). The results are given in Table No. 4.

TABLE NO. 3

EFFECT OF TIME UPON ZONE OF INHIBITION

Compound	Ointment Base	Zone of Inhibition (mm.) 5 days	10 days	15 days
20% Osage Orange Extract	a	5	5	5
	f	12	12	12
5% Undecylenic Acid	a	5	2.5	2
	b	6	1	0
	d	11	6	4
20% Zinc Undecylenate	f	5	3.5	3.5
10% Copper Undecylenate	a	5	4	3
	f	5	3	2
5% 3-Phenylsalicylic Acid	e	7	0	0
	f	1	0	0
8% Copper 3-Phenylsalicylate	a	6	5	4.5
	e	8	8	8
	f	3	3	3
5% Salicylanilide	a	7.5	7.5	7
	c	5	3	3
	e	12	12	12
15% Salicylic Acid	d	5	1	0
	e	16	16	16
	f	6	6	6

a = Hydrophilic Ointment
b = Hydrophilic Petrolatum
c = White Ointment
d = Petrolatum Rose Water Ointment
e = Polyethylene Glycol Ointment
f = Vanishing Cream

TABLE NO. 4

EFFECT OF pH ON FUNGISTASIS

Compound	pH	Zone of Inhibition (mm.) Hydrophilic Ointment	Hydrophilic Petrolatum	Vanishing Cream
5% Undecylenic acid	none	4.2	5.4	3.7
	6	4.0	4.7	3.3
	7	5.3	4.3	3.3
	8	5.3	5.0	3.7
20% Zinc Undecylenate	none	0.2	0.0	4.3
	6	1.0	0.0	4.3
	7	0.7	0.0	5.0
	8	2.7	0.0	5.3
10% Copper Undecylenate	none	4.3	0.1	4.7
	6	6.3	1.7	4.0
	7	6.0	0.3	5.3
	8	7.0	0.6	5.7
5% Salicylanilide	none	6.4	3.7	4.7
	6	4.7	4.2	6.0
	7	5.3	4.3	7.0
	8	5.7	3.7	6.7
5% 3-Phenylsalicylic acid	none	0.0	0.0	0.3
	6	3.4	0.0	1.7
	7	4.7	0.0	2.7
	8	4.3	0.0	3.5
8% Copper 3-Phenylsalicylate	none	5.1	0.0	3.3
	6	10.7	3.0	5.3
	7	11.0	3.5	6.0
	8	11.0	4.0	6.7
20% Osage Orange Extract	none	5.0	0.0	12.3
	6	9.7	0.0	11.3
	7	10.0	0.0	12.7
	8	9.7	0.0	12.3

The addition of the buffer solutions to the ointments appears to be an improvement for 3-phenylsalicylic acid and its copper salt. The activity of osage orange extract in the buffered Hydrophilic Ointment is quite marked, which possibly indicates that the active ingredient is water soluble. Others that show slightly greater activity with the

buffered ointment bases are undecylenic acid, copper and zinc undecylenate in Hydrophilic Ointment, and zinc and copper undecylenate in vanishing cream.

There appears to be a slight negative effect by the inclusion of a buffer in the case of salicylanilide in Hydrophilic Ointment, and the undecylenic acid in Hydrophilic Petrolatum. These results are not in entire agreement with the work reported by Hillegas (4), which demonstrated greater activity of undecylenic acid at pH 8. The differences may be explained by the method employed.

Further tests were made with the osage orange extract. The extract in the vanishing cream base showed a slight separation after a short time. The ointment prepared with 6% of the extract in vanishing cream was stable and was the minimum concentration which gave activity.

Summary

1. The osage orange wood extract did not demonstrate fungicidal activity.

2. The 20% ointment of the extract in a vanishing cream showed marked fungistatic activity. There was moderate activity in Hydrophilic Ointment. The minimum concentration was 6% in Polyethylene Glycol Ointment.

3. The extract prepared by our laboratory demonstrated greater activity than the commercial osage orange wood extract.

4. A comparison of the compounds in various ointment bases showed that Polyethylene Glycol Ointment was the most effective base for the following compounds:

1) 15% salicylic acid
2) 5% salicylanilide
3) 5% undecylenic acid
4) 8% copper 3-phenylsalicylic acid
5) 5% 3-phenylsalicylic acid
6) 5% undecylenic acid with 20% zinc undecylenate
7) 10% copper undecylenate

5. The 20% osage orange extract and 20% zinc undecylenate were most effective in the vanishing cream base.

6. Of the other bases tested, Hydrophilic Ointment, Petrolatum Rose Water Ointment, White Ointment and Hydrophilic Petrolatum were effective in that order.

7. The copper 3-phenylsalicylate and the osage orange extract appeared to be markedly benefited by the addition of the buffer solution to Hydrophilic Ointment. Other compounds appeared to be only slightly benefited.

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(3) "United States Pharmacopeia" Fourteenth Revision, Mack Publishing Co., Easton, Pa., 1950, p. 972.

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SELECTED ABSTRACTS

Streptomycin Resistance in Pulmonary Tuberculosis. Turnbull, F. W. A., Wallace, A. T., Stewart, S., and Crofton, J. W. *Brit. Med. J.* No. 4822-1244 (1953) Little attention has been paid to the possibility of resistant strains emerging following the treatment of pulmonary tuberculosis with sodium or calcium *para*-aminosalicylate (PAS) The authors reported that 9 patients had been treated with PAS alone for periods ranging from 6 weeks to 16 months. Eight of these 9 patients had strains of tubercle bacilli which were resistant to PAS. These patients were then placed on a combined regimen of 1 Gm. streptomycin daily and 20 Gm. PAS daily for at least 3 months. An additional 5 patients, who had not had PAS previously, were placed on the same combined regimen.

Within 3 months 6 of the 8 patients with initially PAS-resistant strains of tubercule bacilli had also developed resistant strains to streptomycin. The other 2 patients had developed streptomycin resistant strains within 1 and 2 additional months. By contrast, only one of the 6 patients with initially PAS-sensitive strains developed a weakly resistant strain to streptomycin.

The implications of these findings are rather obvious, according to the authors. PAS, like streptomycin and isoniazid, should never be administered alone to patients with tuberculosis. It is probably true that streptomycin prevents or diminishes the emergence of PAS-resistant organisms just as PAS prevents or reduces the development of streptomycin resistant organisms. If resistance to PAS has developed from prior single medication and subsequent combined treatment is instituted, PAS will then no longer prevent or reduce the development of streptomycin resistant organisms.

The Treatment of Vivax Malaria with Pyrimethamine. Singh, J., Ray, A. P., Basu, P. C., and Misra, B. G. *Brit. Med. J.* No. 4822:1260 (1953) Little had apparently appeared in the literature with regard to the use of pyrimethamine (Daraprim) in the treatment of vivax malaria The authors reported the results which they obtained in the treatment of 30 cases with a single oral dose of 25 mg. of pyrimethamine.

The patients were divided into two groups, 17 who had had previous attacks of malaria and 13 who had not. The clinical symptoms responded to treatment most rapidly. Nine of the first group and 5 of the second group were afebrile within 24 hours. All of the patients had become afebrile within 72 hours. The asexual parasites had disappeared from the periperal blood within 48 hours in 24 of the patients and within 96 hours in all of the patients. The gametocytes disappeared much more slowly from the peripheral blood of the 23 patients in whom they had been found. They had disappeared in only 9 of the patients after 72 hours. A total of 144 hours was required before the gametocytes disappeared from the peripheral blood of the last of the patients.

It appeared that those who had a previous history of malaria responded more rapidly than those who had not, with respect to clinical symptoms and the disappearance of asexual parasites. The authors also pointed out the smallness of the dose which was effective. They, therefore, concluded that pyrimethamine would appear to have a good future in the treatment of vivax malaria.

Gastric Acid Secretion and Gastric Ulcer Formation of Rats and Guinea Pigs. Ambrus, J. L., Ambrus C. M., and Harrisson, J. W. E. *Am. J. Physiol. 173:*95 (1953). The question of interdigestive gastric secretion has been studied in rats and guinea pigs. In guinea pigs no such secretion was evidenced except a short lasting secretion following any operative procedure. In rats a fairly continuous secretion was observed. This is not due to the cephalic phase of gastric secretion since anesthesia does not abolish it. It is not due to the stimulant action of saliva or regurgitation of duodenal contents since it was present in animals with ligated esophagus and duodenum. The intestinal phase of gastric secretion seems not to be involved since it is present in animals with empty intestines. The lack of gall bladder and the continuous entrance of bile into the duodenum may be a factor, since ligation of the coledochus decreased interdigestive secretion, but did not completely abolish it. Interdigestive secretion was lower in histamine desensitized animals than in normal ones. In previous reports, Ambrus, Ambrus and Jacob: *Experientia 6:*272 (1950); *Arch. Internat. Pharmacodyn. Therap. 86:*350 (1951);

and Ambrus, Ambrus and Harrisson: *Gastroenterology 18:*249 (1951) it has been shown that histamine induced gastric secretion is not decreased by antihistamines but markedly depressed by histamine desensitization. The above results indicate that the mode of action of histamine desensitization in this respect may partly be due to exhaustion of the parietal cells. Histamine desensitization inhibited the formation of gastrointestinal ulcers provoked by the method of Hay *et al.* (*Surg. Gynec. Obst. 75:*170 (1942) in guinea pigs but did not influence gastric ulceration produced by the method of Shay *et al.* (*Gastroenterology 5:*43 (1945) in rats. Antihistamines did not influence gastric ulcer production by these methods. The physiological and pathological significance of the above findings is discussed.

The Treatment of Congestive Heart Failure With Cation Exchange Resin. Lefken, E. B., Hawley, D. K., and Iglauer, A. *Postgrad. Med. 12:*537 (1952). Eight patients with congestive heart failure whose edema tended to recur unless mercurial diuretics were given were studied by the authors in this investigation. The ammonium and potassium cation exchange resin was given in milk in amounts of 15 Gm. along with meals. Mercuhydrin was given intramuscularly to each patient in an amount of 2 cc. on two successive days. One trial was performed while the patient was taking resin and another while he was in the control period.

The authors found that some favorable response was obtained in all of their patients from the administration of the resin. However, the patients with severe congestive heart failure did not respond as well as did the patients who merely had the problem of edema which recurred unless sodium intake was rigidly restricted. The favorable response in 2 patients with severe cardiac failure while taking resin plus a 300 mg. sodium diet suggested that further study with resin in conjunction with a lower sodium diet should be undertaken. The patients with milder failure could be kept comfortable and edema-free while taking the resin with diets containing fairly liberal amounts of sodium. The mercuhydrin injections usually gave better results when combined with the resin. There was also some evidence that mercuhydrin could be reduced or eliminated by the administration of resin.

An important objective of the authors in this study was to seek to determine whether or not there were disturbances in the acid-base balance. However, no disturbance was noted in the blood chemistries of any of the patients. This gives further evidence as to the safety of administration of the cation exchange resins.

Active Immunization Against Poliomyelitis in Human Subjects. Salk, J. E., Bennett, B. L., Lewis, L. J., Ward, E. N., and Youngner, J. S. *J. A. M. A. 151*:1081 (1953). The authors reported that studies had been under way for more than a year with the objective of establishing the conditions necessary for the destruction of the disease-producing property of poliomyelitis virus without destroying its capacity to induce the formation of antibody. Success in this regard in experiments on monkeys led to the work under progress in human beings. This preliminary report was presented to indicate the results thus far obtained.

The virus of each of the 3 immunological types was produced by culturing in monkey testicular tissue or monkey kidney tissue. Before the virus was inoculated into human beings it was rendered non-infectious to monkeys by treatment with formaldehyde. In one series of experiments there was an induction of antibody formation for all 3 immunologic types of virus by the inoculation into human beings of small portions of vaccines prepared as water-in-oil emulsions. In another series of studies, antibody formation was induced by the intradermal inoculation of aqueous vaccine containing type 2 virus. The antibody thus produced had persisted in the body for 4½ months after the beginning of the experiment, the longest period of observation covered by this report.

Comparison of the distribution of antibody titers following vaccination with those in patients who had recently been paralyzed showed good correlation. Thus, it would appear that it should be possible to approximate the immunological result produced by the disease itself by the administration of vaccines.

The authors warned, however, that although the results may be considered to be encouraging they do not indicate that a practical vaccine has now been fully developed. Much further study must be given to the improvement of the safety of the vaccine, to the establishment of the certainty of reproducible results, and to the improvement of the antibody titers obtained.

Evidences for the Safety of the Fluordation of Public Water Supplies. Heyroth, Francis F., *Am. J. Pub. Health 42:* 1568 (1952). The author presented a discussion of the current knowledge of the toxicology of the fluoride ion and its relation to the safety of the fluoridation of public water supplies. A number of studies have been made on animals over prolonged periods of time in order to try to determine the amount of fluoride necessary to cause toxic results. In one case, 2 litter-mate dogs were given 65 mg. of fluoride daily while a third litter-mate served as control. This continued for over 5 years. Although about 10 times the amount of fluoride was found in the bones of the dogs receiving the halide as compared with the dog receiving none, there was no striking evidence of toxic effects in the organs or bones of the dogs.

Cases of human fluorosis from industrial exposure have been recorded on rare occasions. Human volunteer experimentation has also been conducted. In one instance two persons took doses of sodium fluoride equivalent to 3 to 12 mg. of fluoride per day over long periods of time. In neither of these persons did radiographic changes occur in the density of the bones. Studies of the fluoride content of the drinking water of local areas has provided valuable individual and collective data. A study of the food and fluid consumed by a 63-year old man and his 57-year old wife indicated that their daily intake of fluoride was about 15.3 mg., only about 15 per cent of which appeared to be stored. They had lived under essentially this same condition for a number of years. It has also been estimated that over 3 million people in the U. S. use water with from 0.9 to 5.1 ppm. of fluoride.

The author concluded by stating that the results of animal experimentation and the study of human beings experimentally or naturally exposed to rather large quantities of fluoride give consistent evidence that bringing the fluoride content of community water supplies to a level known to be optimal for dental health is a prophylactic measure which has an ample margin of safety.

The Effect of Alumina Gel on the Blood Level of an Oral Sulfonamide. Berkowitz, Donald, *Antibiotics & Chemother. 3:*618 (1953). The effect of the administration of an oral triple sulfonamide preparation in a vehicle of alumina gel as compared with an identical preparation without the alumina gel was studied by the author.

Thirty-two subjects, whose renal and hepatic functions were adjudged to be normal, were given the alumina gel suspension containing 0.167 Gm. each of sulfadiazine, sulfamerazine, and sulfamethazine per 5 cc. Twenty-seven subjects received the identical preparation except without the alumina gel. Thirty subjects were given either sulfisoxazole or sulfadimetine in tablet form. All of the preparations were given in an initial dose of 4 Gm. total sulfonamide followed by 1 Gm. every 6 hours, except for sulfisoxazole which was given in a dose of 2 Gm. every 6 hours.

The therapeutic blood level was taken to be 10 mg. per 100 cc. The average total sulfonamide level exceeded 10 mg. with the triple alumina preparation only, and for a period of about the second hour through the 12th hour. However, the plain triple preparation showed an average level of between 9 and 10 mg. This level was maintained from about the third through the 10th hour after the initial dose. Neither sulfisoxazole nor sulfadimetine exceeded slightly more than 8 mg. per cent. Seventy-six per cent of the patients receiving the triple alumina preparation had therapeutic blood levels after 6 hours as compared with 44 per cent of those who received the plain triple preparation. Even after 14 hours, 26 per cent of the former had therapeutic blood levels, but none of the latter had a therapeutic blood level after 10 hours.

Thus, it would appear that the alumina gel vehicle raised the blood level and prolonged the duration obtained following the oral administration of a triple sulfonamide suspension as compared with a preparation which was identical in composition except that it contained no alumina gel.

Treatment of Tuberculosis With Isoniazid. Tuberculosis Chemotherapy Trials Committee of the Medical Research Council (England). *Brit. Med. J.* No. 4809:521 (1953). The Council studied the therapy of tuberculosis in 364 patients spread over 40 hospitals. The therapeutic implements included a combination of streptomycin and isoniazid, streptomycin and PAS, or isoniazid alone. Therapy was given over a three-month period. The condition of most of the patients improved during the period of treatment but the differences among the three types of treatment were small.

The combination of streptomycin and isoniazid was slightly superior to the other treatments. Weight gain was strikingly better, the lowering of temperature in patients with pyrexia, and the lowering of sedimentation rate was better with the streptomycin and isoniazid combination. Little difference was observed in the radiological response between the two combinations, but both combinations produced better response than did isoniazid alone. The proportions of patients having negative sputum samples after the three months of therapy were 67 per cent for those receiving the streptomycin and isoniazid treatment, 55 per cent for those receiving the streptomycin and PAS, and 37 per cent for those receiving isoniazid alone.

Resistance did not develop to streptomycin, isoniazid, nor PAS during the three-month period when the combinations were given. However, patients who had strains of organisms which were resistant initially to one of the combination pair were apparently not protected from the danger of the development of resistance to the other member of the pair also.

The Council also concluded that none of the therapeutic agents studied should be administered alone. Whenever possible, the drug sensitivity of the organisms infecting a patient should be determined before therapy is begun and, then, a combination selected which should be effective.

BOOK REVIEWS

Chymia. Volume 4. 217 pages including index. University of Pennsylvania Press, 3436 Walnut Street, Philadelphia 4, Pa., 1953. $4.50.

This annual set of studies in the history of chemistry is a part of the Edgar F. Smith Memorial Collection of the University of Pennsylvania.

Volume 4, well illustrated and with excellent typography, is a splendid addition to the three preceding sets. All of the authors are scholars in their fields, and, to the reader who likes history, many new and unusual facts are available herein.

Subjects covered in this volume include the origin of alchemy, Madame Lavoisier, Benjamin Rush, Robert Boyle, Auguste Laurent, Charles Caldwell and Maxwell Simpson.

This book is excellent for reference and reading.

JOHN E. KRAMER

Encyclopedia of Chemical Reactions, Vol. IV. By C. A. Jacobson, West Virginia University, Editor. 790 pages, incl. index. Reinhold Publishing Corporation. 330 W. 42nd Street, New York, N. Y., 1951. Price $14.00.

This is the fourth volume in a series which is to include the entire field of chemical reactions. This volume covers the elements iron, lanthanum, lead, lithium, magnesium, manganese, mercury, molybdenum, and neodymium. It follows the general form of the previous volumes.

The Encyclopedia of Chemical Reactions fills a real need for an authoritative reference work, and should be on the shelves of every chemical library.

LOUIS A. REBER

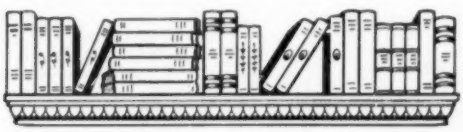
Textbook of Organic Chemistry, Third Edition. By George Holmes Richter, Dean of The Rice Institute and Professor of Organic Chemistry. John Wiley and Sons, Inc., 440 Fourth Ave., New York 16, N. Y., 1952. vii-762 pp. 16 x 23.5 cm. Price $6.75.

This third edition of the well known text has been expanded to include many new reactions and some of the modern theories of organic chemistry. Such material as the Leuckart and Mannich reactions, use of radioactive carbon in synthetic work, silicon polymers, cortisone, penicillin, mechanism of reaction of unsaturated systems, treatment of molecular orbitals and many other interesting topics not to be found in an elementary text are expertly written. For example, the chapter on alkyl halides and Grignard reaction contain a wealth of information on the scope and limitations, conditions of reaction, etc., which represents a very complete summary of what to expect from this reaction. The same could be said for almost every chapter in the book.

The text is amply illustrated with formulae, diagrams, tables and charts, but this does not lead to incoherency as the material is presented in a form which is very easy to read. Questions are included at the end of each chapter and appear to cover the subject matter very completely, which would appeal to the instructional aspect of organic chemistry.

In all, Dr. Richter has again come forth with an outstanding text and reference book which is a concise treatise on the enormous field of organic chemistry.

A. GENNARO



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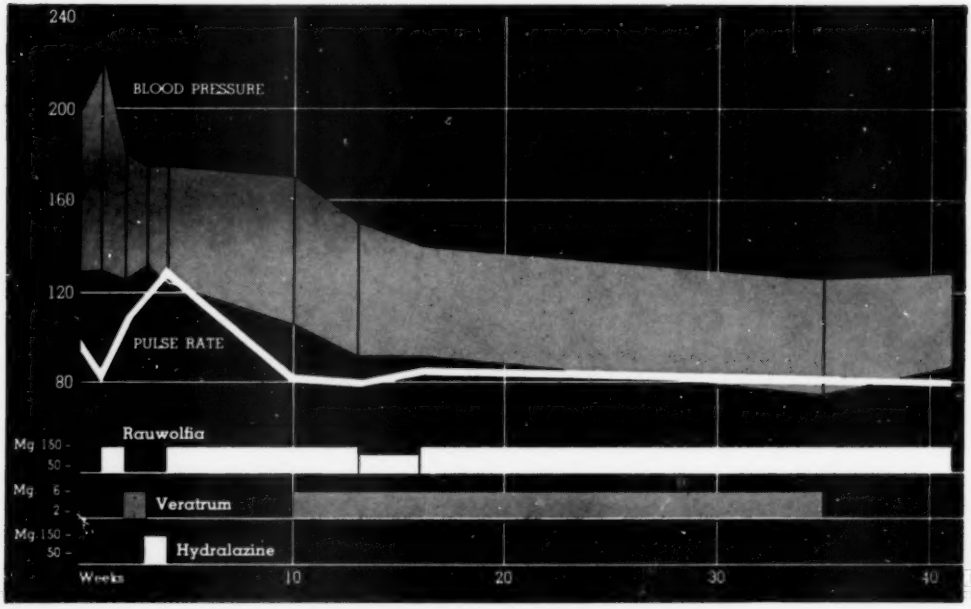

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